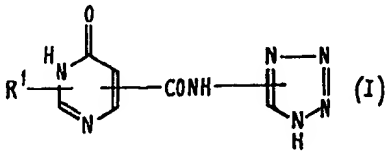
(12) UK Patent Application (19) GB (11) 2 095 240 A

(21) Application No 8205929
(22) Date of filing 1 Mar 1982
(30) Priority data
(31) 8106902
(32) 5 Mar 1981
(33) United Kingdom (GB)
(43) Application published
29 Sep 1982
(51) INT CL³
C07D 403/12 A61K
31/505 C07D 239/36
(52) Domestic classification
C2C 1464 1510 1530
1601 215 220 226 22Y
246 247 248 250 251 252
254 258 25Y 280 281
28X 292 29Y 30Y 313
31Y 321 323 32Y 332 338
342 34Y 350 351 352 364
365 366 367 36Y 386 388
604 621 623 624 625 628
62X 634 661 662 678
699 761 762 802 80Y AA
KR KS MM TA TR
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicant
Fujisawa Pharmaceutical
Co. Ltd.,
No. 3 Doshomachi,
4-chome,
Higashi-ku,
Osaka,
Japan
(72) Inventors
Tsutomu Teraji,
Teruo Oku,
Takayuki Namiki,
Norihiko Shimazaki
(74) Agents
Stevens, Hewlett and
Perkins,
5 Quality Court,
Chancery Lane,
London,
WC2A 1HZ

(54) **Dihydropyrimidine derivatives, processes for preparation thereof and pharmaceutical composition comprising the same**

(57) Dihydropyrimidine derivatives having the formula



(I)

wherein R^1 is pyridyl, thienyl or optionally substituted aryl, and their pharmaceutically-acceptable salts have anti-allergic activity in human beings and animals.

GB 2 095 240 A

Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Dihydropyrimidine derivatives, processes for preparation thereof and pharmaceutical composition comprising the same

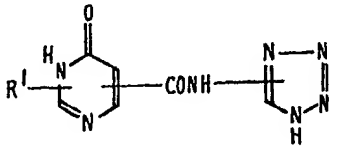
This invention relates to dihydropyrimidine derivatives. More particularly, it relates to dihydropyrimidine derivatives which have antiallergic activity, processes for the preparation thereof and a pharmaceutical composition comprising the same and to a method of use of the same in treatment of symptoms associated with allergic manifestations in human beings or animals.

Accordingly, it is an object of this invention to provide new dihydropyrimidine derivatives which are useful as an antiallergic agent.

Another object of this invention is to provide processes for preparing the dihydropyrimidine derivatives.

Further object of this invention is to provide a pharmaceutical composition comprising the dihydropyrimidine derivatives.

Dihydropyrimidine derivatives of this invention include the compound represented by the following formula:



(I)

wherein

R^1 is pyridyl, thienyl, or aryl which may bear one or more substituent(s) selected from the group of halogen, hydroxy, nitro, amino, di(lower)alkylamino, lower alkoxy and ar(lower)alkoxy, and pharmaceutically acceptable salts thereof.

Particulars of the above definitions and suitable examples thereof are explained as follows.

As to the term "lower" used in the specification and claims, it is to be understood that it means the one having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable aryl for R^1 may be phenyl, tolyl, xylyl, naphthyl and the like.

Suitable halogen for the substituent of the aryl group may be fluorine, chlorine, bromine and iodine.

Suitable di(lower)alkylamino for the substituent of the aryl group may be dimethylamino, diethylamino, dipropylamino, diisopropylamino, methylethylamino, dibutylamino and the like.

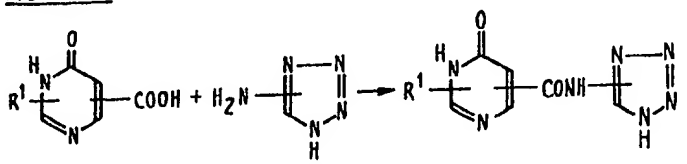
Suitable lower alkoxy for the substituent of the aryl group may be methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, hexyloxy and the like.

Suitable "ar(lower)alkoxy" for the substituent of the aryl group may be benzyloxy, phenethyloxy, benzhydryloxy, trityloxy and the like.

Suitable pharmaceutically acceptable salts of the compound (I) may be a salt with an inorganic or organic base (e.g. sodium salt, potassium salt, calcium salt, magnesium salt, trimethylamine salt, ethanolamine salt, etc.) and an acid addition salt (e.g. hydrochloride, sulfate, nitrate, maleate, acetate, etc.).

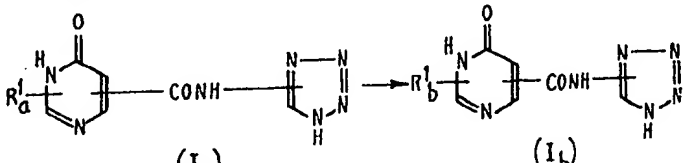
Dihydropyrimidine derivatives of this invention can be prepared by various processes as illustrated below.

Process 1:



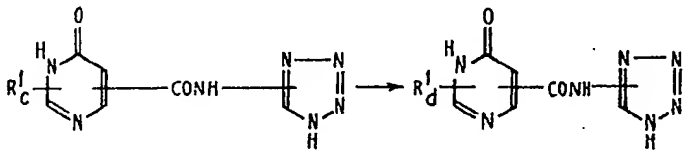
(II) (III) (I)

Process 2:



(I_a) (I_b)

Process 3:



(I_c) (I_d)

wherein

R^1 is the same as defined above,

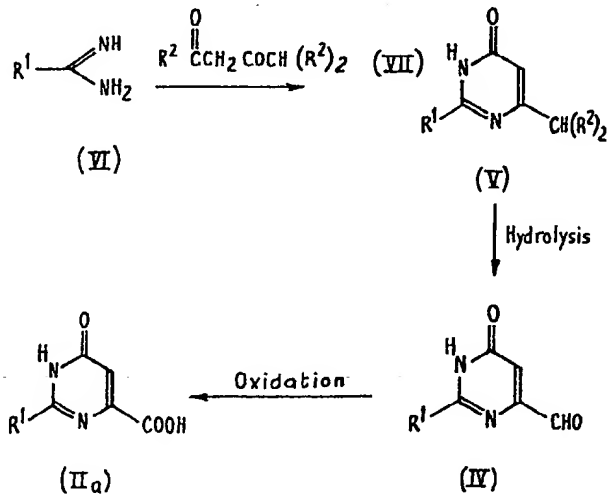
R^1_a is aryl having a protected hydroxy group,

R^1_b is aryl having a hydroxy group,

R^1_c is aryl having a nitro group, and

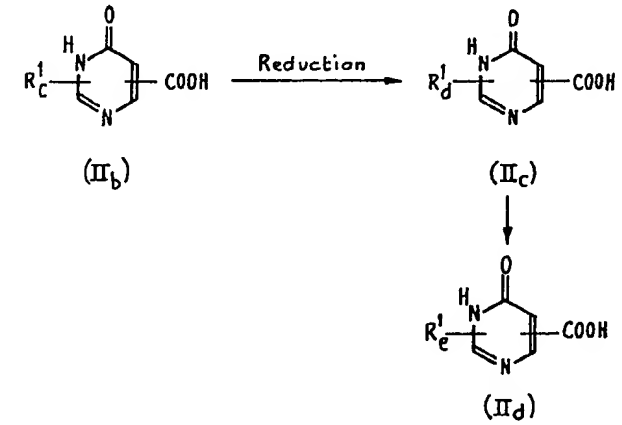
R^1_d is aryl having an amino group.

Among the starting compounds (II), some novel compounds can be prepared by the following Preparations (A) and (B) and the others can be prepared by a similar manner thereto.



(VI) (VII) (V) (II_a) (IV)

Preparation (B)



(II_b) (II_c) (II_d)

wherein

R^1, R^1_c and R^1_d are each as defined above,

R^1_e is aryl having di(lower)alkylamino, and

R^2 is lower alkoxy.

The processes as illustrated above are explained in detail in the followings.

Process 1:

The object compound (I) or its salt can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group with the compound (III) or its salt.

Suitable reactive derivatives of the compound (II) may be a conventional ones such as an acid halide, acid azide, an acid anhydride, an activated amide, an activated ester and the like.

Suitable salts of the compound (III) may be an acid addition salt (e.g. hydrochloride, etc.).

When the starting compound (II) is used in a form of free acid, the reaction of this process may preferably be conducted in the presence of a condensing agent such as carbodiimidic compound (e.g. N,N'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.), N,N'-carbonyldi-(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, alkoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus compound (e.g. phosphorus oxychloride, phosphorus trichloride, etc.), thionyl chloride, oxalyl chloride, 2-ethyl-7-hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide, (chloromethylene)-dimethylammonium chloride, 2,2,4,4,6,6-hexachloro-1,3,5,2,4,6-triazatriphosphorine, 1-benzenesulphonyloxy-6-chloro-1H-benzotriazole, p-toluenesulfonyl chloride, isopropoxybenzenesulfoxyl chloride, or a mixed condensing agent such as triphenylphosphine and a carbon tetrahalide (e.g. carbon tetrachloride, carbon tetrabromide, etc.) or a complex of N,N-dimethylformamide with phosphoryl chloride, phosgene or thionyl chloride, etc., and the like.

The reaction is usually conducted in a solvent such as acetone, diethyl ether, dioxane, acetonitrile, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, chloroform, pyridine, N-methylmorpholine, N-methylpyrrolidine, etc. or a mixture thereof.

The reaction temperature is not critical and this reaction can be conducted within the temperature range of cooling to heating.

Process 2:

The object compound (I_b) or its salt can be prepared by removing the protective group of the compound (I_a) or its salt.

The reaction conditions for removing the protective group may be selected according to the kind of the protective group. For instance, ar(lower)alkyl as a protective group can preferably be removed by catalytic reduction.

The catalytic reduction is usually conducted at ambient temperature or under cooling in an inert solvent (e.g. N,N-dimethylformamide, ethanol, propanol, isobutyl alcohol, tetrahydrofuran, chloroform, ethyl acetate, acetic acid, etc.) by using a conventional catalyst such as Raney nickel, palladium on carbon, or the like.

Process 3:

The compound (I_d) or its salt can be prepared by reducing the compound (I_c) or its salt.

This reduction can also be carried out by a catalytic reduction.

The conditions of the catalytic reduction are the same as explained in the above Process 2.

Preparation (A)

(1) Preparation of the compound (V)

The compound (V) can be prepared by reacting the compound (VI) or its salt with the compound (VII).

Suitable lower alkoxy for R^2 of the starting compound (VII) is the same as exemplified before.

Suitable salts of the starting compound (VI) may be an inorganic or organic acid addition salt such as hydrochloride, sulfate, nitrate, trifluoroacetate, and the like.

This reaction can be conducted in an inert solvent such as methanol, ethanol, propanol, N,N-dimethylformamide, dimethylsulfoxide and the like, under ice cooling—at ambient temperature.

(2) Preparation of compound (IV)

The compound (IV) can be prepared by hydrolyzing the compound (V).

This hydrolysis can preferably be conducted in the presence of inorganic or organic acid such as hydrochloric acid, sulfuric acid, nitric acid, formic acid, acetic acid and the like.

The hydrolysis is usually conducted in an inert solvent such as water, acetone and the like, at ambient temperature—under heating.

(3) Preparation of the compound (II_a)

The compound (II_a) or its salt can be prepared by oxidizing the compound (IV).

The oxidation can be carried out by using an oxidizing agent such as silver oxide, silver nitrate, potassium permanganate, and the like.

This oxidation can preferably be carried out in the presence of an inorganic or organic base (e.g. sodium hydroxide etc.)

The reaction is usually carried out in an inert solvent such as methanol, tetrahydrofuran, water and the like at ambient temperature—under heating.

Preparation (B)

(1) Preparation of the compound (II_c)

The compound (II_c) or its salt can be prepared by reducing the compound (II_b) or its salt.

This reduction can preferably be carried out by a catalytic reduction.

The conditions of the catalytic reduction are the same as those explained in the above Process 2.

(2) Preparation of the compound (II_d)

The compound (II_d) or its salt can be prepared by alkylating the compound (II_c) or its salt.

The alkylation can be carried out by reacting the compound (II_c) or its salt with di(lower)alkylketone (e.g. acetone, etc.) or alkanal (e.g. formaldehyde, acetaldehyde, etc.) in the presence of a reducing agent such as a reducing agent containing boron in its molecule (e.g. sodium borohydride, sodium cyanoborohydride, etc.).

This reaction is usually carried out in an inert solvent such as water, methanol, ethanol, tetrahydrofuran and the like, at ambient temperature—under warming.

The object compound (I), (I_b) and (I_d) in the Process 1—3 can be isolated, purified and optionally converted into their salt in a conventional manner.

The object compound, dihydropyrimidine derivatives (I) have an antiallergic activity. Accordingly, the object compound of this invention is useful for the treatment of symptoms associated with allergic diseases such as allergic asthma, allergic rhinitis, urticaria, pollenosis, allergic conjunctivitis, atopic dermatitis, ulcerative colitis, alimentary allergy (e.g. milk allergy), bird fancier's disease, aphthous stomatitis and the like. For illustrating purpose, the antiallergic activity of representative compound of the object compounds (I) shown in the followings.

Test I

[Inhibitory effect on PCA (Passive Cutaneous Anaphylaxis) reaction]

(1) Test compound

Sodium salt of 1,6-dihydro-6-oxo-2-(4-hydroxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]carboxamide.

(2) Test method

(a) Preparation of antiserum

A solution of egg albumin (2 mg) in B pertussis-diphtheria-tetanus mixed vaccine (1 ml) was mixed with Freund incomplete adjuvant (1 ml) to give an emulsion. The emulsion was given subcutaneously in a single dose of 1 ml divided equally (0.25 ml) to the four foot pads of male SD (Sprague-Dawley) strain rats aged 8 weeks, each weighing about 300 g.

10 days after the immunization, blood samples were collected from femoral artery of the rats and allowed to stand under ice-cooling for 5 hours. The separated supernatant was centrifuged at 4°C (10,000 r.p.m. x 1 hour). The antisera thus obtained were stored at —80°C prior to use.

(b) Inhibitory effect on P.C.A.

Male SD-strain rats aged 8 weeks, weighing 290 to 330 g, were used for PCA reaction with the homologous reaginic antiserum as prepared above. Each 0.1 ml of 32 fold diluted antiserum were injected intradermally at separate sites on the back of rats clipped free of hair, and 48 hours later, 1 ml of aqueous solution containing each 5 mg of the egg albumin and Evans blue was injected intravenously to evoke PCA reaction. Test compound was given to the animals intravenously 5 minutes before the challenge with antigen. Control group received vehicle. Each dose group consisted of 5 animals. One hour after the challenge with antigen, the animals were sacrificed and then skinned. Dye spots caused with antiserum were investigated for their size on the reversed side of the skin, respectively. The results were expressed by per cent inhibition values calculated from averaged values of the longest and shortest diameters for each spot in comparison with those in control group.

(3) Test results

Test results are shown in the following table.

Dose of the Test Compound	*Inhibitory effect (%)*
1 mg/kg	100
0.1 mg/kg	62.5

The dihydropyrimidine derivatives (I) of this invention can be used as an active antiallergic agent either in free form or in a form of the pharmaceutically acceptable salt.

The object compound (I) and its pharmaceutically acceptable salt can usually be administered to mammals including human beings in the form of a conventional pharmaceutical composition such as capsule, microcapsule, tablet, granule, powder, troche, syrup, aerosol, inhalation, solution, injection, suspension, emulsion, suppository, ointment, or the like.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycole-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, aerosil, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, mentol, ammonium salt of grycyrlysine, glycine, orange powders, etc.), preservative (sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent [e.g. polysolbate 80, emalgen 408 (surface active agent), emasol (surface active agent), etc.], aqueous diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, witepsol, white petrolatum, etc.).

A dosage of the present active ingredient is to be varied depending on various factors such as weight and/or age of a patient and/or a stage of the allergic disease, and further the kind of administration route. In general, an effective dosage may be in a range of about 20—2000 mg/day for an oral route, about 2.5—250 mg/day for an intramuscular or intravenous injection, about 10—1000 mg/day for a subcutaneous injection and about 120 mg—2000 mg/day for a rectal route. The total daily amount mentioned above may be divisionally given to the patient at the interval of 6—12 hours per day. Preferable single dose of the present active ingredient may be, for example, about 10—500 mg per tablet or capsule, about 1.25—250 mg per vial or ampoule, or about 60—500 mg per suppository, and so on, and further a pharmaceutical form for an external use may be, for example, about 1—10% ointment, solution or emulsion, etc.

The following Examples are given for the purpose of illustrating this invention.

Example 1

(1) To a solution of dry methanol (43 ml) containing sodium methoxide (prepared from 0.506 g of sodium metal) was added 4-benzyloxybenzamidine methylsulfate (3.22 g.) under cooling in an ice bath and stirring. After stirring for 10 minutes, methyl γ,γ-dimethoxyacetoacetate (1.94 g.) was dropped over 2 minutes thereto. The mixture was stirred in an ice bath for 30 minutes and then at ambient temperature for 24 hours. The resulting mixture was adjusted to pH 4 with 10% hydrochloric acid and stirred in an ice bath for 10 minutes. The precipitates were collected by filtration, washed with water, and dried to give 3.23 g of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal. m.p. 194 to 196.5°C.

I.R. (nujol): 1660, 1605, 1595 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 3.34 (s, 6H), 5.14 (s, 1H), 5.20 (s, 2H), 6.47 (s, 1H), 7.16 (d, J=9Hz, 2H), 7.44 (m, 5H), 8.17 (d, J=9Hz, 2H), 12.67 (bs, 1H)

(2) A mixture of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)-pyrimidine-4-carbaldehyde dimethyl acetal (14.14 g) and formic acid (58 ml) was stirred at ambient temperature for 30 minutes and then at 60 to 65°C for 2.5 hours. After cooling of the reaction mixture, the precipitates was filtered, washed with acetone and dried to give 11.92 g of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)-pyrimidine-4-carbaldehyde. m.p. 244 to 245°C.

I.R. (nujol) : 3150, 3075, 1715, 1645, 1600 cm^{-1}

(3) To a solution of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-carbaldehyde (0.9 g) in 1/2N aqueous sodium hydroxide (12 ml) was added potassium permanganate (0.47 g) in the course of 10 minutes under cooling in an ice bath and stirring and the stirring was continued at ambient temperature for one hour, followed by filtration. The filtrate was washed five times with ethyl acetate, adjusted to pH 1 with 10% hydrochloric acid and allowed to stand for a while. The precipitates were filtered, washed with water and dried to give 0.80 g of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-carboxylic acid. m.p. 253.5 to 254°C (dec.)

I.R. (nujol) : 2600, 2475, 2350, 1710, 1645 cm^{-1}

(4) To a suspension of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-carboxylic acid (2.91 g) in N,N-dimethylformamide (29 ml) was added N-N'-carbonyldiimidazole (1.65 g) in one portion at ambient temperature. The mixture was stirred for 5 minutes at ambient temperature and for 35 minutes at 90°C, followed by addition of 5-aminotetrazole (1.08 g). The resulting mixture was stirred for an hour at 90°C and cooled slowly to ambient temperature. The precipitates were collected

by filtration, washed with ethanol and dried to give 3.36 g of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide. m.p. 298 to 301°C (dec.)

I.R. (nujol) : 3225, 2675, 2575, 1685, 1675, 1600 cm^{-1}

N.M.R. ($NaOD+D_2O$) δppm : 5.20 (s, 2H), 6.74 (s, 1H), 6.90 (d, J=9Hz, 2H), 7.22 (s, 5H), 8.08 (d, J=9Hz, 2H)

Anal. Calcd. for $C_{19}H_{15}N_7O_3$: C; 58.61, H; 3.88, N; 25.18
found: C; 59.05, H; 5.94 N; 25.46

(5) A solution of 1,6-dihydro-6-oxo-2-(4-benzyloxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide (1.8 g) in water (54 ml) and 1N-aqueous sodium hydroxide (10 ml) containing 10% palladium on charcoal (0.6 g) was hydrogenated at 3.45 atmosphere hydrogen pressure.

After the calculated amount of hydrogen was absorbed, the catalyst was separated by filtration and washed with water. The combined filtrates were acidified with 10% hydrochloric acid. The precipitates were filtered, washed several times with water and purified by recrystallization from water (250 ml) containing sodium bicarbonate (1.70 g) to give 1.38 g of sodium salt of 1,6-dihydro-6-oxo-2-(4-hydroxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide. m.p. 300°C.

I.R. (nujol): 2600, 1660, 1595 cm^{-1}

N.M.R. ($NaOD+D_2O$) δppm: 6.78 (d, J=9Hz, 2H), 6.82 (s, 1H), 8.14 (d, J=9Hz, 2H)

Anal. Calcd. for $C_{12}H_8O_3N_7N_a \cdot 3H_2O$: C; 38.41, H; 3.76, N; 26.13
found: C; 38.11, H; 3.96, N; 26.03

Example 2

(1) 1,6-Dihydro-6-oxo-2-phenylpyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 163 to 165°C (Recrystallization from ethyl acetate)

I.R. (nujol): 3150, 1660, 1605 cm^{-1}

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C; 63.40 H; 5.73, N; 11.38
found: C; 63.43, H; 5.82, N; 11.26

N.M.R. ($CDCl_3$) δppm: 3.48 (6H, s), 5.26 (1H, s), 6.75 (1H, s), 7.60—8.33 (5H, m)

(2) To a suspension of 1,6-dihydro-6-oxo-2-phenylpyrimidine-4-carbaldehyde dimethyl acetal (6.62 g) in acetone (60 ml) and dichloromethane (100 ml) was added conc. hydrochloric acid (14 ml) in one portion at ambient temperature. The mixture was stirred for 17 hours and concentrated to 20 ml, followed by the addition of water (50 ml). The aqueous layer was adjusted to pH 8 with an aqueous solution saturated with sodium bicarbonate. The separated solid was filtered, washed with water and dried under reduced pressure to give 3.88 g of 1,6-dihydro-6-oxo-2-phenylpyrimidine-4-carbaldehyde. m.p. 204 to 205°C.

I.R. (nujol): 3400, 1670, 1660, 1605 cm^{-1}

(3) To a suspension of 1,6-dihydro-6-oxo-2-phenyl-pyrimidine-4-carbaldehyde (6.0 g) in ethanol (100 ml) was added a solution of silver nitrate (7.74 g) in water (10 ml) at ambient temperature. After stirring for a few minutes, a solution of potassium hydroxide (5.6 g) in water (95 ml) was added dropwise over a interval of 15 minutes thereto. The reaction temperature was maintained below 30°C during the addition. The mixture was filtered to remove an insoluble materials, which were washed with water (50 ml). The filtrate was acidified with 10% hydrochloric acid and the precipitates were collected by filtration. This solid was dissolved in aqueous sodium bicarbonate and an insoluble materials were filtered off. The filtrate was acidified with 10% hydrochloric acid. The precipitates were collected by filtration, washed with water and dried to give 3.20 g of 1,6-dihydro-6-oxo-2-phenylpyrimidine-4-carboxylic acid. m.p. >270°C.

I.R. (nujol): 3050, 2500, 1700, 1650, 1600 cm^{-1}

(4) To a suspension of 1,6-dihydro-6-oxo-2-phenyl-pyrimidine-4-carboxylic acid (2.59 g) in N,N-dimethylformamide (26 ml) was added N,N'-carbonyldiimidazole (2.13 g) in one portion at ambient temperature. The mixture was stirred for 5 minutes at ambient temperature and then for 40 minutes at 90°C, followed by addition of 5-aminotetrazole (1.19 g). The resulting mixture was stirred for an hour at 90°C and cooled slowly to ambient temperature. The precipitates were collected by filtration and washed with water. After drying, the precipitates were recrystallized from water (140 ml) containing sodium bicarbonate (3.36 g) to yield 1.26 g of sodium salt of 1,6-dihydro-6-oxo-2-phenylpyrimidine-4-[N-(5-tetrazolyl)]-carboxamide. m.p. >270°C.

I.R. (nujol): 3250, 1700 (shoulder), 1650 cm^{-1}

Anal. Calcd. for $C_{12}H_8N_7O_2N_a$: C; 47.22, H; 2.64, N; 32.12
found: C; 47.07, H; 2.79, N; 31.96

Example 3

(1) 1,6-Dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 114 to 117°C.

I.R. (nujol): 3150, 1670, 1590 cm^{-1}

N.M.R. ($CDCl_3$) δppm: 1.63 (3H, t, J=7Hz), 3.48 (6H, s), 4.38 (2H, t, J=7Hz), 5.28 (1H, s), 6.68 (1H, s), 7.00—8.60 (4H, m), 11.50 (1H, bs)

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C; 62.05, H; 6.25, N; 9.65
found: C; 61.99. H; 6.03, N; 9.98

(2) 1,6-Dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 167 to 170°C.

I.R. (nujol): 3250, 1710, 1665, 1580 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. >270°C.

I.R. (nujol: 3200, 2500, 1720, 1645 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >270°C.

I.R. (nujol): 3350, 2500, 1700, 1660 cm^{-1}

Anal. Calcd. for $C_{14}H_{13}N_7O_3$: C; 51.37, H; 4.00, N; 29.96
found: C; 51.41, H; 3.71, N; 30.12

Example 4

(1) 1,6-Dihydro-6-oxo-2-(2-pyridyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 132°C.

I.R. (nujol): 3100, 1650, 1610 cm^{-1}

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C; 58.29, H; 5.30, N; 17.00
found: C; 58.33, H; 5.41, N; 17.03

N.M.R. ($CDCl_3$) δppm: 3.46 (6H, s), 5.20 (1H, s), 6.68 (1H, s), 7.33—8.76 (4H, m), 11.10 (1H, s)

(2) 1,6-Dihydro-6-oxo-2-(2-pyridyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 141 to 143°C.

I.R. (nujol): 3250, 1650, 1595 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(2-pyridyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. >270°C.

I.R. (nujol): 3350, 2500, 1735, 1675, 1595 cm^{-1}

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(2-pyridyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >270°C.

I.R. (nujol): 3500, 3200, 1655, 1600 cm^{-1}

Anal. Calcd. for $C_{11}H_7O_2N_8N_a \cdot 1/2\ H_2O$: C; 41.91, H; 2.56, N; 35.54
found: C; 41.75, H; 2.86, N; 35.75

Example 5

(1) 1,6-Dihydro-6-oxo-2-(3-pyridyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 179 to 183°C.

I.R. (nujol): 2400, 1605, 1590 cm^{-1}

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C; 58.29, H; 5.30, N; 17.00
found: C; 58.30, H; 5.33, N; 16.89

N.M.R. (DMSO—d_6) δppm: 3.40 (6H, s), 5.22 (1H, s), 6.50 (1H, s), 7.58—9.31 (4H, m)

(2) 1,6-Dihydro-6-oxo-2-(3-pyridyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 168°C (dec.).

I.R. (nujol): 3200, 1715, 1670, 1600 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(3-pyridyl)-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. >270°C.

I.R. (nujol): 2500, 1660, 1610 cm^{-1}

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(3-pyridyl)-pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >270°C.

I.R. (nujol): 3250, 1680, 1610 cm^{-1}

Example 6

(1) 1,6-Dihydro-6-oxo-2-(4-pyridyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 208 to 209°C.

I.R. (nujol): 1665, 1590 cm^{-1}

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C; 58.29, H; 5.30, N; 17.00
found: C; 58.39, H; 5.36, N; 16.79

N.M.R. (DMSO—d_6) δppm.: 3.30 (6H, s), 5.15 (1H, s) 6.50 (1H, s), 8.05 (2H, d, J=7Hz), 8.73 (2H, d, J=7Hz)

(2) 1,6-Dihydro-6-oxo-2-(4-pyridyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 273 to 274°C (dec.).

I.R. (nujol): 1725, 1610 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-pyridyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. 274 to 275°C.

I.R. (nujol): 3450, 3150, 1670, 1640 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(4-pyridyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >270°C.

I.R. (nujol): 3150, 1680, 1605 cm^{-1}

Anal. Calcd. for $C_{11}H_8O_2N_8 \cdot H_2O$: C; 43.71, H; 3.33, N; 37.07
found: C; 43.83, H; 3.43, N; 37.09

N.M.R. (D_2O+N_aOD) δppm: 6.82 (1H; s), 8.12 (2H, d, J=6Hz), 8.64 (2H, d, J=6Hz)

Example 7

(1) 1,6-Dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 218 to 220°C (Recrystallization from chloroform-methanol, 220—222°C).

I.R. (nujol): 3050, 1660, 1600 cm^{-1}

Anal. Calcd. for $C_{15}H_{18}O_5N_2$: C; 58.81, H; 5.92, N; 9.15
found: C; 58.89, H; 6.07, N; 9.10

N.M.R. ($CDCl_3$) δppm: 3.41 (6H, s), 3.96 (3H, s), 4.05 (3H, s), 5.18 (1H, s), 6.56 (1H, s), 7.00 (1H, d, J=9Hz), 7.91 (1H, s), 8.00 (1H, d, J=9Hz)

(2) A mixture of 1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal (10.81 g), acetone (100 ml), conc. hydrochloric acid (10 ml), and water (5 ml) was refluxed for 2.25 hours. The mixture was cooled to ambient temperature and the precipitates were collected by filtration, followed by washing with acetone to yield 1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)-pyrimidine-4-carbaldehyde hydrochloride (7.96 g). m.p. 267 to 268°C.

I.R. (nujol): 3050, 2500, 1685, 1655, 1610 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 270°C.

I.R. (nujol): 3300, 2500, 1745, 1650 cm^{-1}

(4) To a suspension of 1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-carboxylic acid in N,N-dimethylformamide (27 ml) was added N,N'-carbonyldiimidazole (1.78 g) in one portion at ambient temperature and the mixture was stirred at 80 to 90°C for 30 minutes followed by an addition of 5-aminotetrazole (1.10 g). The resulting mixture was stirred at 80 to 90°C for one hour and cooled in an ice bath. The precipitates were collected by filtration, washed with dimethylformamide and dried to give 1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide (2.26 g). This product was dissolved in 1N aqueous sodium hydroxide solution and a small amount of insoluble materials were filtered off. After an addition of ethanol to the filtrate, the resulting precipitates were collected by filtration, washed with 80% aqueous ethanol and dried to yield disodium salt of 1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide (1.66 g). m.p. >270°C.

I.R. (nujol): 3300, 1695, 1610 cm^{-1}

Anal. Calcd for $C_{14}H_{11}O_4Na_2 \cdot 1—1/2\ H_2O$: C; 40.58, H; 3.40, N; 23.66
found: C; 40.52, H; 3.90, N; 23.94

Example 8

(1) 1,6-Dihydro-6-oxo-2-(o-tolyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 164 to 167°C.

I.R. (nujol): 3050, 1680, 1605 cm^{-1}

(2) 1,6-Dihydro-6-oxo-2-(o-tolyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 203 to 205°C.
I.R. (nujol): 2800, 1700, 1650, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(o-tolyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 250 to 252°C (dec.) (Recrystallization from aqueous 70% dimethylformamide).
I.R. (nujol): 2500, 1715, 1640, 1595 cm^{-1}
Anal. Calcd. for $C_{12}H_{10}O_3N_2$: C; 62.60, H; 4.38, N; 12.17
found: C; 62.48, H; 4.48, N; 12.16

Example 9
(1) 1,6-Dihydro-6-oxo-2-(4-chlorophenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 223 to 227°C.
I.R. (nujol): 3050, 1655, 1595 cm^{-1}
N.M.R ($CDCl_3$) δppm: 3.42 (6H, s), 5.20 (1H, s), 6.70 (1H, s), 7.51 (2H, d, J=8Hz), 8.25 (2H, d, J=8Hz)
Anal. Calcd for $C_{13}H_{13}O_3N_2Cl$: C; 55.62, H; 4.66, N; 9.98
Found: C; 55.38, H; 4.69, N; 9.91

(2) 1,6-Dihydro-6-oxo-2-(4-chlorophenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 200 to 202°C.
I.R. (nujol): 1690, 1670 (shoulder), 1600 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-chlorophenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. >270°C (recrystallization from dimethylformamide-diethylether)
I.R. (nujol): 3450, 1740 (shoulder), 1690, 1650, 1595 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(4-chlorophenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >270°C (Recrystallization from dimethylformamide)
I.R. (nujol): 3100, 1675, 1590 cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 6.76 (1H, s), 7.26 (2H, d, J=8Hz), 7.98 (2H, d, J=8Hz)
Anal. Calcd. for $C_{12}H_{18}O_2N_7Cl \cdot 1/2\ H_2O$: C; 44.12, H; 2.77, N; 29.99
found: C; 44.20, H; 2.42, N; 29.97

Example 10
(1) 1,6-Dihydro-6-oxo-2-(4-nitrophenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 259 to 260°C.
I.R. (nujol): 1650 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 3.34 (6H, s), 5.22 (1H, s), 6.55 (1H, s) 8.35 (4H, s)

(2) 1,6-Dihydro-6-oxo-2-(4-nitrophenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 287.5 to 288°C (dec.)
I.R. (nujol): 1710, 1650, 1610 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-nitrophenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 263 to 264°C.
I.R. (nujol): 3050, 2500, 1730 (shoulder), 1700, 1640, 1610 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(4-nitrophenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >300°C.
I.R. (nujol): 3625, 3450, 1670 cm^{-1}

(5) A solution of 1,6-dihydro-6-oxo-2-(4-nitrophenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide (1.83 g) in water (73 ml) and sodium bicarbonate (1.41 g) containing 10% palladium on charcoal (0.74 g) was hydrogenated at 3.5 atmosphere. After the calculated amount of hydrogen was absorbed, the catalyst was separated by filtration and washed with water. The combined filtrates were acidified with 10% hydrochloric acid. The precipitates were collected by filtration, washed several times with water and purified by recrystallization from water (250 ml) containing sodium bicarbonate (2 g) to give 1.72 g of sodium salt of 1,6-dihydro-6-oxo-2-(4-aminophenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide. m.p. >300°C.
I.R. (nujol): 3375, 3250, 3100, 1725, 1685, 1600 cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 6.55 (2H, d, J=9Hz) 6.63 (1H, s), 7.74 (2H, d, J=9Hz)
Anal. Calcd. for $C_{12}H_9N_8O_2N_a \cdot 2H_2O$: C; 40.42, H; 3.65, N; 31.46
found: C; 40.49, H; 3.41, N; 31.66

Example 11

(1) 1,6-Dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 161 to 162°C.

I.R. (nujol): 1660, 1605 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 1.30 (6H, d J=6Hz), 3.35 (6H, s), 4.74 (1H, m), 5.14 (1H, s), 6.30 (1H, s), 7.03 (2H, d, J=9Hz), 8.11 (2H, d, J=9Hz), 12.45 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 226 to 268°C (dec.) (Recrystallization from ethyl acetate)

I.R. (nujol): 3075, 1720, 1645, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 254 to 254.5°C (dec.) (recrystallization from dimethylformamide)

I.R. (nujol): 1755, 1640, 1600 cm^{-1}

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C; 61.31 H; 5.14, N; 10.21
Found: C; 61.34, H; 5.00, N; 10.29

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(4-isopropoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.

I.R. (nujol): 3300, 3075, 1715 (shoulder), 1685, 1605 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 1.30 (6H, d, J=6Hz), 4.76 (1H, m), 6.94 (1H, s), 7.07 (2H, d, J=9Hz), 8.41 (2H, d, J=9Hz)

Anal. Calcd. for $C_{15}H_{14}N_7O_3Na \cdot H_2O$: C; 47.24, H; 4.19, N; 25.72
found: C; 46.56, H; 4.10, N; 26.13

Example 12

(1) 1,6-Dihydro-6-oxo-2-(m-tolyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 178 to 179°C.

I.R. (nujol): 1655, 1550 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 2.40 (3H, s), 3.34 (6H, s), 5.17 (1H, s), 6.37 (1H, s), 7.43 (2H, m), 7.97 (2H, m), 12.67 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(m-tolyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 215 to 225°C (dec.) (Recrystallization from methyl alcohol)

I.R. (nujol): 3275, 1670, 1600 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(m-tolyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 258 to 258.5°C (dec.) (Recrystallization from dimethylformamide)

I.R. (nujol): 3075, 2575, 2450, 1705, 1635, 1570 cm^{-1}

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C; 62.61, H; 4.38, N; 12.17
found: C; 62.73, H; 4.29, N; 12.37

(4) 1,6-Dihydro-6-oxo-2-(m-tolyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of 1 (4). m.p. >300°C.

I.R. (nujol): 3350, 3150, 1680, 1575 cm^{-1}

N.M.R. (D_2O+$N_a HCO_3$) δppm: 2.06 (3H, s). 6.58 (1H, s), 6.98 (2H, m), 7.58 (2H, m)

Anal. Calcd. for $C_{13}H_{11}N_7O_2 \cdot 1/2H_2O$: C; 50.98, H; 3.94, N; 32.01
found: C; 51.28, H; 4.16, N; 32.47

Example 13

(1) 1,6-Dihydro-6-oxo-2-(2-thienyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 213 to 215°C (dec.)

I.R. (nujol): 3075, 1650 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 3.40 (6H, s), 5.16 (1H, s), 6.36 (1H, s), 7.27—8.23 (3H, m), 12.74 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(2-thienyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. >300°C.

I.R. (nujol): 3300, 3075, 1680 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(2-thienyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 254 to 254.5°C (dec.) (Recrystallization from dimethylformamide)

I.R. (nujol): 3080, 2600, 2450, 1730, 1675, 1640 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(2-thienyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >300°C.
I.R. (nujol): 3300, 3075, 1700 (shoulder), 1680, 1650 (shoulder), 1580, 1555 cm^{-1}
N.M.R. ($D_2O+N_aHCO_3$) δppm: 6.52 (1H, s), 6.74—7.52 (3H, m)
Anal. Calcd. for $C_{10}H_7N_7O_2S\cdot 1/4H_2O$: C; 40.84, H; 2.55, N; 33.37
found: C; 40.94, H; 2.35, N; 33.13

Example 14

(1) 1,6-Dihydro-6-oxo-2-(p-tolyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 197 to 198°C (Recrystallization from ethyl alcohol)
I.R. (nujol): 1650, 1595 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 2.38 (3H, s), 3.32 (6H, s), 5.12 (1H, s), 6.32 (1H, s), 7.30 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz), 12.74 (1H, br s)
Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C; 64.60, H; 6.20, N; 10.76
found: C; 65.05, H; 6.30, N; 10.74

(2) 1,6-Dihydro-6-oxo-2-(p-tolyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 207 to 244°C (dec.)
I.R. (nujol): 3375, 1715, 1655, 1610, 1590

(3) 1,6-Dihydro-6-oxo-2-(p-tolyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 255.5 to 260°C (dec.)
I.R. (nujol): 1760, 1645, 1590 cm^{-1}
Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C; 62.61, H; 4.38, N; 12.17
found: C; 62.20, H; 4.46, N; 12.20

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(p-tolyl)-pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.
I.R. (nujol): 3300, 3050, 1715, 1680, 1595 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 2.38 (3H, s), 6.90 (1H, s), 7.34 (2H, d, J=8Hz), 8.30 (2H, d, J=8Hz)
Anal. Calcd. for $C_{13}H_{10}N_7O_2N_a\cdot 2H_2O$: C; 43.95, H; 3.97, N; 27.60
found: C; 43.45, H; 3.85, N; 27.41

Example 15

(1) 1,6-Dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 205 to 206°C (Recrystallization from ethanol)
I.R. (nujol): 1660, 1605 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 3.32 (6H, s), 3.82 (3H, s), 5.10 (1H, s), 6.28 (1H, s), 7.06 (2H, d, J=9Hz), 8.10 (2H, d, J=9Hz), 12.68 (1H, br s)
Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C; 60.86, H; 5.84, N; 10.14
found: C; 60.63, H; 5.92, N; 9.96

(2) 1,6-Dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 229 to 232°C. (Recrystallization from dimethylformamide)
I.R. (nujol): 3075, 1710, 1665, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 2 (3). m.p. 249 to 250°C (dec.)
I.R. (nujol): 2575, 2475, 1705, 1645, 1610 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(4-methoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4), m.p. >300°C.
I.R. (nujol): 3275, 3075, 1710, 1680, 1605, 1545 cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 3.85 (3H, s), 6.65 (1H, s), 7.07 (2H, d, J=9Hz), 8.10 (2H, d, J=9Hz)
Anal. Calcd. for $C_{13}H_{10}N_7O_3N_a\cdot 2H_2O$: C; 42.06, H; 3.80, N; 26.41
found: C; 42.27, H; 3.51, N; 26.94

Example 16

(1) A solution of 1,6-dihydro-6-oxo-2-(4-nitrophenyl)-pyrimidine-4-carboxylic acid (4 g) and sodium bicarbonate (3.84 g) in water (200 ml) containing 10% palladium on charcoal (2 g) was hydrogenated at 3.4 atmosphere hydrogen pressure. After being agitated for 3 hours, the mixture was warmed and the catalyst was separated by filtration followed by washing with water. The filtrate was adjusted to pH 3 to 4 with 10% hydrochloric acid. The precipitates were collected, washed with water

and dried to give 1.76 g of 1,6-dihydro-6-oxo-2-(4-aminophenyl)pyrimidine-4-carboxylic acid. m.p. 264 to 267°C. (dec.)
I.R (nujol): 3300, 2600, 1630 cm^{-1}

(2) To a suspension of 1,6-dihydro-6-oxo-2-(4-aminophenyl)pyrimidine-4-carboxylic acid (2.0 g) in methanol (356 ml) was added acetic acid (71 ml) and 37% aqueous formaldehyde (7.13 ml) successively. After being stirred at room temperature for 15 minutes, sodium cyanoborohydride (1.65 g) was added in one portion. The resulting mixture was stirred at ambient temperature for 5 hours. The precipitates were collected, washed with methanol and water, and dried to yield 1.82 g of 1,6-dihydro-6-oxo-2-(4-dimethylaminophenyl)pyrimidine-4-carboxylic acid. m.p. 270°C (dec.)
I.R. (nujol): 1750, 1635, 1600 cm^{-1}

(3) Sodium salt of 1,6-dihydro-6-oxo-2-(4-dimethylaminophenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.
I.R. (nujol): 3600, 3325, 3075, 1690, 1650, 1610 cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 2.70 (6H, s), 6.44 (2H, d, J=9Hz), 6.64 (1H, s), 7.79 (2H, d, J=9Hz)
Anal. Calcd. for $C_{14}H_{13}N_8O_2N_a \cdot H_2O$: C; 45.90, H; 4.12, N; 30.59
found: C; 45.50, H; 3.97, N; 30.81

Example 17

(1) 1,6-Dihydro-6-oxo-2-(4-methoxy-3-methylphenyl)-pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 216 to 217°C.
I.R. (nujol): 3150, 3050, 1655, 1610 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 2.20 (3H, s), 3.33 (6H, s), 3.87 (3H, s), 5.10 (1H, s), 6.24 (1H, s), 7.04 (1H, d, J=10Hz), 8.00 (2H, m), 12.45 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(4-methoxy-3-methylphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 258.5 to 259°C (dec.)
I.R. (nujol): 3150, 3050, 1715, 1670, 1610 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-methoxy-3-methylphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. 264°C, (dec.)
I.R. (nujol): 3050, 1700, 1640, 1605 cm^{-1}

(4) 1,6-Dihydro-6-oxo-2-(4-methoxy-3-methylphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 1 (4). m.p. >300°C.
I.R. (nujol): 3475, 3150, 1675, 1610 (shoulder) cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 1.90 (3H, s), 3.58 (3H, s), 6.51 (1H, d, J=10Hz), 6.58 (1H, s), 7.65 (2H, m)
Anal. Calcd. for $C_{14}H_{13}N_7O_3 \cdot 1/2H_2O$: C; 49.95, H; 4.16, N; 29.10
found: C; 49.65, H; 4.15, N; 28.97

Example 18

(1) 1,6-Dihydro-6-oxo-2-(4-ethoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 198 to 199°C.
I.R. (nujol): 3150, 1660, 1610, 1595 cm^{-1}
N.M.R. (DMSO—d_6) δppm: 1.35 (3H, t, J=7Hz), 3.34 (6H, s), 4.15 (2H, q, J=7Hz), 5.14 (1H, s), 6.30 (1H, s), 7.08 (2H, d, J=9Hz), 8.15 (8H, d, J=9Hz), 12.67 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(4-ethoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 239 to 240°C.
I.R. (nujol): 1710, 1680, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-ethoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. 238 to 239°C. (dec.)
I.R. (nujol): 3075, 2600, 2475, 1710, 1645, 1610 cm^{-1}

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(4-ethoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.
I.R. (nujol): 3375, 1705, 1610, 1550 cm^{-1}
N.M.R. (D_2O+N_aOD) δppm: 1.34 (3H, t, J=7Hz), 4.06 (2H, q, J=7Hz), 6.74 (1H, s), 7.00 (2H, d, J=9Hz), 8.08 (2H, d, J=9Hz)
Anal. Calcd. for $C_{14}H_{12}N_7O_3N_a \cdot H_2O$: C; 45.74, H; 3.81, N; 26.68
Found: C; 45.13, H; 3.79, N; 26.81

Example 19

(1) 1,6-Dihydro-6-oxo-2-(4-butoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 158 to 159°C.

I.R. (nujol): 3125, 3050, 1655, 1605 cm^{-1}

N.M.R. ($CDCl_3$) δppm: 1.00 (3H, m), 1.67 (4H, m) 3.42 (6H, s), 4.03 (2H, t, J=6Hz), 5.17 (1H, s), 6.62 (1H, s), 6.98 (2H, d, J=9Hz), 8.22 (2H, d, J=9Hz), 12.78 (1H, br s)

(2) 1,6-Dihydro-6-oxo-2-(4-butoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (1). m.p. 215 to 216°C.

I.R. (nujol): 3150, 3075, 1705, 1655, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-butoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. 246°C. (dec.) (Recrystallization from dimethylformamide)

I.R. (nujol): 2580, 2475, 1710, 1645, 1610 cm^{-1}

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(4-butoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.

I.R. (nujol): 3325, 3075, 1720, 1690, 1605 cm^{-1}

N.M.R. (N_aOD+D_2O) δppm: 0.84 (3H, t, J=7Hz), 1.00—1.80 (4H, m), 3.72 (2H, t, J=6Hz), 6.78 (2H, d, J=9Hz), 6.82 (1H, s), 8.06 (2H, d, J=9Hz)

Anal. Calcd. for $C_{16}H_{16}N_7O_3N_a \cdot 1H_2O$: C; 48.61, H; 4.59, N; 24.80

found: C; 48.44, H; 4.61, N; 24.92

Example 20

(1) 1,6-Dihydro-6-oxo-2-(4-propoxyphenyl)pyrimidine-4-carbaldehyde dimethyl acetal was obtained according to similar manner to that of Example 1 (1). m.p. 167 to 168°C.

I.R. (nujol): 3150, 3075, 1670, 1655 (shoulder), 1605 1595 cm^{-1}

N.M.R. (DMSO—d_6) δppm: 1.00 (3H, t, J=7Hz), 1.77 (2H, m), 3.35 (6H, s), 4.02 (2H, t, J=7Hz), 5.13 (1H, s), 6.30 (1H, s), 7.05 (2H, d, J=9Hz), 8.13 (2H, d, J=9Hz)

(2) 1,6-Dihydro-6-oxo-2-(4-propoxyphenyl)pyrimidine-4-carbaldehyde was obtained according to similar manner to that of Example 2 (2). m.p. 198 to 199°C.

I.R. (nujol): 3150, 3075, 1710, 1655, 1605 cm^{-1}

(3) 1,6-Dihydro-6-oxo-2-(4-propoxyphenyl)pyrimidine-4-carboxylic acid was obtained according to similar manner to that of Example 1 (3). m.p. 248°C (dec.) (Recrystallization from dimethylformamide)

I.R. (nujol): 2575, 2475, 1710, 1655 (shoulder), 1645, 1610 cm^{-1}

(4) Sodium salt of 1,6-dihydro-6-oxo-2-(4-propoxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]-carboxamide was obtained according to similar manner to that of Example 2 (4). m.p. >300°C.

I.R. (nujol): 3300, 3075, 1720, 1685, 1610 cm^{-1}

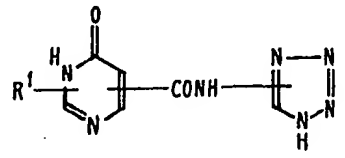
N.M.R. (N_aOD+D_2O) δppm: 0.90 (3H, t, J=7Hz), 1.60 (2H, m), 3.62 (2H, t, J=6Hz), 6.64 (2H, d, J=8Hz), 6.76 (1H, s), 7.90 (2H, d, J=8Hz)

Anal. Calcd for $C_{15}H_{14}N_7O_3N_a \cdot 1/2H_2O$: C; 48.39, H; 4.06, N; 26.33

found: C; 48.48, H; 3.90, N; 26.48

Claims

1. Dihydropyrimidine derivatives of the formula.



(I)

wherein

R^1 is pyridyl, thienyl, or aryl which may bear one or more substituent(s) selected from the group of halogen, hydroxy, nitro, amino, di(lower)alkylamino, lower alkoxy and ar(lower) alkoxy,

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, in which R^1 is pyridyl, thienyl or phenyl which may bear one or more substituent(s) selected from the group of halogen, hydroxy, nitro, amino, di(lower)alkylamino, lower alkoxy and phenyl(lower)alkoxy.

3. A compound according to claim 2, in which R^1 is pyridyl, thienyl, phenyl, halophenyl,

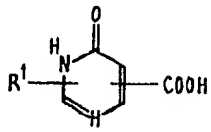
hydroxyphenyl, nitrophenyl, aminophenyl, di(lower)alkylaminophenyl, mono or di(lower)alkoxyphenyl or phenyl(lower)alkoxyphenyl.

4. A compound according to claim 2, in which R^1 is hydroxyphenyl.

5. A compound according to claim 2, which is 1,6-dihydro-6-oxo-2-(4-hydroxyphenyl)pyrimidine-4-[N-(5-tetrazolyl)]carboxamide or a pharmaceutically acceptable salt thereof.

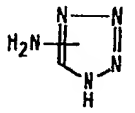
6. A process for preparing a compound of claim 1, which comprises,

a) reacting a compound of the formula:



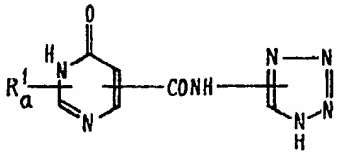
wherein

R^1 is the same as defined above, or its reactive derivative at the carboxy, with a compound of the formula:



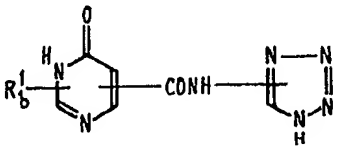
or its salt to give a compound (I) or its salt; or

b) subjecting a compound of the formula:



wherein

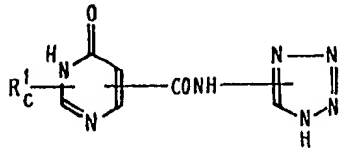
R_a^1 is aryl having a protected hydroxy group, or its salt, to catalytic reduction to give a compound of the formula:



wherein

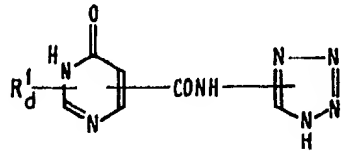
R_b^1 is aryl having a hydroxy group or its salt; or

c) reducing a compound of the formula:



wherein

R_c^1 is aryl having a nitro group or its salt to give a compound of the formula:



wherein

R_d^1 is aryl having an amino group, or its salt.

7. A pharmaceutical composition for the treatment of allergic disease in human beings or animals comprising a compound (I) of claim 1 or pharmaceutically acceptable salt thereof as an active ingredient, and a pharmaceutically acceptable carrier.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.